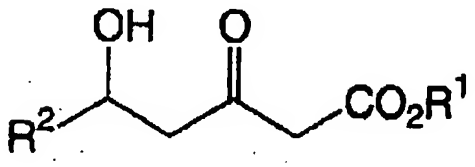
Claims PTO
Claim 1

AMENDMENTS TO THE CLAIMS

In the claims:

Please amend the claims as follows:

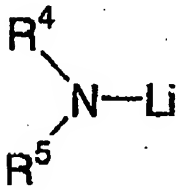
1. (Twice Amended) A process for producing a 5-hydroxy-3-oxopentanoic acid derivative of the following formula (IV):



(IV)

wherein R^1 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and R^2 represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group,

which comprises [permitting] adding a lithium amide of the following formula (III):

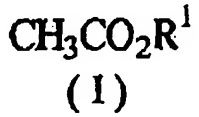


(III)

wherein R^4 and R^5 may be the same or different and each represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms, an aralkyl group of 7 to 12 carbon atoms and a silyl group,

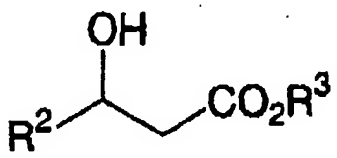
to [act upon] a mixture of an acetic acid ester of the following formula (I) and a 3-hydroxypropionic acid

derivative of the following formula (II) at a temperature not below -20 ℃ to conduct reaction:



(I)

wherein R^1 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms:



(II)

wherein R^2 represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group; R^3 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and R^2 and R^3 may be joined to each other to form a ring, in the presence of a magnesium halide.

Preliminary Amdt

Docket No.: 21581-00240-US
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Nishiyama et al.

Reissue Application No. Not Assigned

Patent No.: 6,340,767 B1

Filed: Herewith

Issued: January 22, 2002

For: PROCESS FOR THE PREPARATION OF 5-HYDROXY-3-OXOPENTANOIC ACID DERIVATIVES

Claims 1-3, 5-18 are pending

PRELIMINARY AMENDMENT

MS REISSUE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

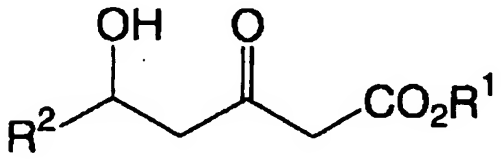
Please amend the application as discussed below.

In The Claims:

Please cancel claims 4, 19 and 20.

Please amend the claims as follows:

1. (Amended) A process for producing a 5-hydroxy-3-oxopentanoic acid derivative of the following formula (IV):

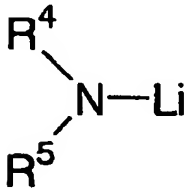


(IV)

wherein R^1 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and R^2 represents any

of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group,

which comprises permitting a lithium amide of the following formula (III):



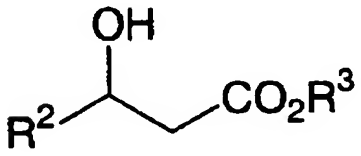
(III)

wherein R^4 and R^5 may be the same or different and each represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms, an aralkyl group of 7 to 12 carbon atoms and a silyl group,

to act upon a mixture of an acetic acid ester of the following formula (I) and a 3-hydroxypropionic acid derivative of the following formula (II) at a temperature not below -20 ℃:

(I)

wherein R^1 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms:



(II)

wherein R^2 represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl

group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group; R^3 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and R^2 and R^3 may be joined to each other to form a ring, in the presence of a magnesium halide.

[4. The process according to Claim 1 wherein a magnesium halide is added in permitting the lithium amide to act.]

5. (Amended) The process according to Claim [4]1 wherein magnesium chloride is used as the magnesium halide.

[19. The process according to Claim 2 wherein a magnesium halide is added in permitting the lithium amide to act.]

[20. The process according to Claim 3 wherein a magnesium halide is added in permitting the lithium amide to act.]

REMARKS

Claims 1-3 and 5-18 are now in the application. Claim 1 has been amended to recite "in the presence of a magnesium halide". This recitation finds support in original patent at col. 7, line 65 to col. 8, line 3. In view of the amendment to claim 1, claims 4, 19 and 20 have been canceled. The amendments to the claim do not introduce any new matter.

In view of the above allowance is respectfully requested.

Dated: 11-12-03

Respectfully submitted,

By _____

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Application No.: 10/705,665 Docket No.: 21581-00240-US1

AMENDMENTS TO THE CLAIMS

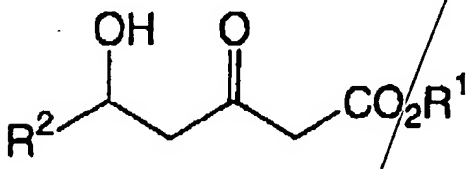
Claims PTO

In the claims:

Please amend the claims as follows:

Claims 6, 10, 17, 18

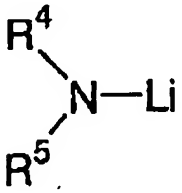
1. (Twice Amended) A process for producing a 5-hydroxy-3-oxopentanoic acid derivative of the following formula (IV):



(IV)

wherein R^1 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and R^2 represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group,

which comprises [permitting] adding a lithium amide of the following formula (III):



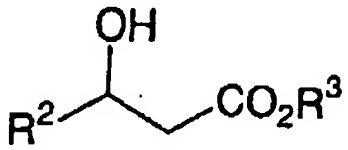
(III)

wherein R^4 and R^5 may be the same or different and each represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms, an aralkyl group of 7 to 12 carbon atoms and a silyl group,

to [act upon] a mixture of an acetic acid ester of the following formula (I) and a 3-hydroxypropionic acid derivative of the following formula (II) at a temperature not below -20°C to conduct reaction:

$CH_3CO_2R^1$ (I)

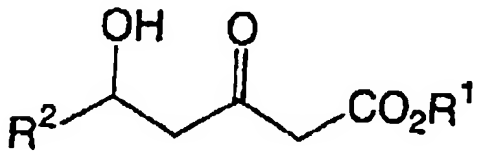
wherein R^1 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms:



(II)

wherein R^2 represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a sustituent, a cyano group, a carboxyl group and an alkoxycarbonyl group; R^3 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and R^2 and R^3 may be joined to each other to form a ring, in the presence of a magnesium halide.

6. (Amended) A process for producing a 5-hydroxy-3-oxopentanoic acid derivative of the following formula (IV):



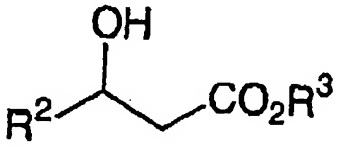
(IV)

wherein R^1 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and R^2 represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to

12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group, which comprises treating a mixture of an acetic acid ester of the following formula (I) and a 3-hydroxypropionic acid derivative of the following formula (II):

$$CH_3CO_2R^1 \qquad (I)$$

wherein R^1 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms:



(II)

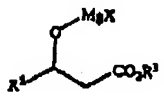
wherein R^2 represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group; R^3 represents any of an alkyl group of 1 to 12 carbon atoms, aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and R^2 and R^3 may be joined to each other to form a ring,

with a Grignard reagent of the following formula (V):

$$R^6\text{-Mg-X} \qquad (V)$$

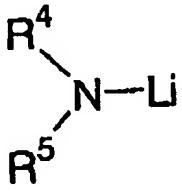
wherein R^6 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and X represents halogen,

to prepare a mixture of a compound of the following formula (VI) and an acetic acid ester of the above formula (I):



(VI)

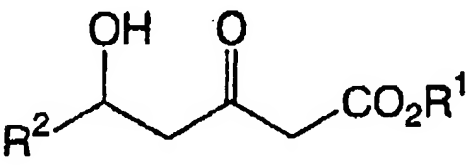
wherein R^2 represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group; R^3 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; R^2 and R^3 may be joined to each other to form a ring; and X represents a halogen atom, and [permitting] adding a lithium amide of the following formula (III):



(III)

wherein R^4 and R^5 may be the same or different and each represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms, an aralkyl group of 7 to 12 carbon atoms and a silyl group
to [act upon] the mixture at a temperature not below -20° C to conduct reaction.

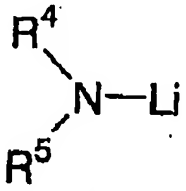
10.(Amended) A process for producing a 5-hydroxy-3-oxopentanoic acid derivative of the following formula (IV):



(IV)

wherein R^1 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and R^2 represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a subtituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group,

which comprises [permitting] adding a lithium amide of the following formula (III):



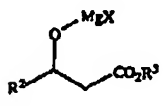
(III)

wherein R^4 and R^5 may be the same of different and each represents any of any alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms, an aralkyl group of 7 to 12 carbon atoms and a silyl group,

to [act upon] a mixture of an acetic acid ester of the following formula (I) and a compound of the following formula (VI) at a temperature not below -20° C to conduct reaction:

$CH_3CO_2R^1$ (I)

wherein R^1 represents any of an alkyl group of 1 to 2 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms:



(VI)

wherein R^2 represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group; R^3 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; R^2 and R^3 may be joined to each other form a ring; and X represents a halogen atom.

17.(amended) The process according to claim 1, wherein the [compound (II) or (VI)] <u>the 3-hydroxypropionic acid derivative of the formula (II) or the 5-hydroxy-3-oxopentanoic acid derivative of the formula (IV)</u> is optically active.

18. (amended) The process according to claim 2 wherein, referring to the acetic acid ester <u>of the formula (I)</u>, R^1 represents a tert-butyl group.

In 8.0 ml of tetrahydrofuran were suspended 1.02 g (10 mmol) of (3S)-3-hydroxybutyrolactone and 2.32 g (20 mmol) of tert-butyl acetate, and the suspension was stirred in an argon atmosphere at 0 to 5° C. To this solution, the above lithium diisopropylamide solution was added dropwise over 30 minuets, and the mixture was further stirred at 5 to 20° C. for 16 hours.

In a separate vessel, 35 mL of 3 N-hydrochloric acid and 30 mL of ethyl acetate were mixed together under stirring and the above reaction mixture was poured. After standing, the organic layer was separated, washed with saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was then distilled off under reduced pressure.

The residue was purified by silica gel column chromatography (Merck's Kieselgel 60, hexane:ethyl acetate=2:1) to give 124 mg of tert-butyl (5S)-5,6-dihydroxy-3-oxohexanoate (yellow oil) in 6% yield.

^{1}H-NMR ($CDCl_3$, 400 MHz/ppm): 1.48 (9H, s), 2.668–2.83 (2H, m), 3.0–3.8 (2H, bs), 3.42 (2H, s), 4.02–4.17 (2H, m), 4.40 (1H, m)

^{13}C-NMR ($CDCl_3$, 400 MHz/ppm): 27.8, 45.7, 51.0, 65.6, 68.0, 82.3, 166.4, 203.4

Example 10

Tert-butyl (5S)-5,6-dihydroxy-3-oxohexanoate

Under argon gas, a solution composed of 3.90 g (38.5 mmol) of diisopropylamine and 3 mL of tetrahydrofuran was added dropwise to 22.9 mL (35 mmol) of n-butyllithium/hexane (1.5 mol/L) with stirring at 5° C. and the mixture was stirred for 1 hour to prepare a lithium diisopropylamide solution.

In 3.0 mL of tetrahydrofuran were dissolved 1.02 g (10 mmol) of (3S)-3-hydroxybutyrolactone and 2.32 g (20 mmol) of tert-butyl acetate, and the solution was stirred in an argon atmosphere at 0 to 5° C. To this solution was added 5.7 g (10 mmol) of a solution of tert-butylmagnesium chloride in toluene/tetrahydrofuran (1:2.5, by weight) (1.75 mol/kg) dropwise over 10 minutes, and the mixture was further stirred at 5° C. for 50 minutes. Then, the lithium diisopropylamide solution prepared above was added dropwise over 30 minutes and the mixture was further stirred at 5 to 20° C. for 16 hours.

In a separate vessel, 30 mL of 3 N-hydrochloric acid and 30 mL of ethyl acetate were mixed together under stirring and the above reaction mixture was poured. After standing, the organic layer was separated, washed with saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was then distilled off under reduced pressure.

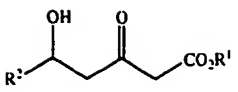
The residue was purified by silica gel column chromatography (Merck's Kieselgel 60, hexane:ethyl acetate=2:1) to give 980 mg of tert-butyl (5S)-5,6-dihydroxy-3-oxohexanoate (red oil) in 48% yield.

INDUSTRIAL APPLICABILITY

The present invention, constituted as described above, enables the production of 5-hydroxy-3-oxopentanoic acid derivatives, which are of use as pharmaceutical intermediates, particularly intermediates of HMG-CoA rductase inhibitors, from inexpensive, readily available starting compounds at a non-very-low temperature.

What is claimed is:

1. A process for producing a 5-hydroxy-3-oxopentanoic acid derivative of the following formula (IV):



(IV)

wherein R^1 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and R^2 represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group,

which comprises permitting a lithium amide of the following formula (III):

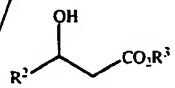
(III)

wherein R^4 and R^5 may be the same or different and each represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms, an aralkyl group of 7 to 12 carbon atoms and a silyl group,

to act upon a mixture of an acetic acid ester of the following formula (I) and a 3-hydroxypropionic acid derivative of the following formula (II) at a temperature not below −20° C.:

(I)

wherein R^1 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms:



(II)

wherein R^2 represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group; R^3 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and R^2 and R^3 may be joined to each other to form a ring.

2. The process according to claim 1

wherein, referring to the lithium amide, R^4 and R^5 each represents an isopropyl group.

3. The process according to claim 1

wherein, referring to the acetic acid ester, R^1 represents a tert-butyl group.

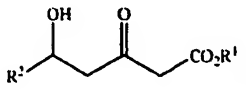
4. The process according to claim 1,

wherein a magnesium halide is added in permitting the lithium amide to act.

5. The process according to claim 4

wherein magnesium chloride is used as the magnesium halide.

6. A process for producing a 5-hydroxy-3-oxopentanoic acid derivative of the following formula (IV):



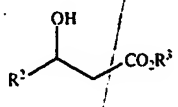
(IV)

wherein R^1 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and R^2 represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group,

which comprises treating a mixture of an acetic acid ester of the following formula (I) and a 3-hydroxypropionic acid derivative of the following formula (II):

(I)

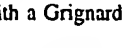
wherein R^1 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms:



(II)

wherein R^2 represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group; R^3 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and R^2 and R^3 may be joined to each other to form a ring,

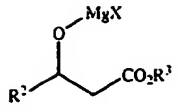
with a Grignard reagent of the following formula (V):



(V)

wherein R^6 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and X represents halogen,

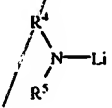
to prepare a mixture of a compound of the following formula (VI) and an acetic acid ester of the above formula (I):



(VI)

wherein R^2 represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group; R^3 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; R^2 and R^3 may be joined to each other to form a ring; and X represents a halogen atom,

and permitting a lithium amide of the following formula (III):



(III)

wherein R^4 and R^5 may be the same or different and each represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms, an aralkyl group of 7 to 12 carbon atoms and a silyl group

to act upon the mixture at a temperature not below −20° C.

7. The process according to claim 6

wherein, referring to the lithium amide, R^4 and R^5 each is an isopropyl group.

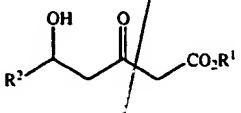
8. The process according to claim 6

wherein, referring to the acetic acid ester, R^1 represents a tert-butyl group.

9. The process according to claim 6,

wherein, referring to the Grignard reagent, R^6 represents a tert-butyl group and X represents a chlorine atom.

10. A process for producing a 5-hydroxy-3-oxopentanoic acid derivative of the following formula (IV):



(IV)

wherein R^1 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and R^2 represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group,

which comprises permitting a lithium amide of the following formula (III):

(III)

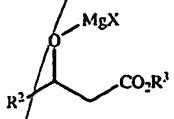
wherein R^4 and R^5 may be the same or different and each represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms, an aralkyl group of 7 to 12 carbon atoms and a silyl group,

to act upon a mixture of an acetic acid ester of the following formula (I) and a compound of the following formula (VI) at a temperature not below −20° C.:

$$CH_3CO_2R^1 \quad (I)$$

wherein R^1 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms:

(VI)



wherein R^2 represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group; R^3 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; R^2 and R^3 may be joined to each other to form a ring: and X represents a halogen atom.

11. The process according to claim 10

wherein, referring to the lithium amide, R^4 and R^5 each represents an isopropyl group.

12. The process according to claim 10

wherein, referring to the acetic acid ester, R^1 represents a tert-butyl group.

13. The process according to claim 10,

wherein, referring to the compound (VI), X represents a chlorine atom.

14. The process according to claim 1

wherein R^3 is a methyl group or an ethyl group.

15. The process according to claim 1

wherein R^2 is a chloromethyl group, a cyanomethyl group or a benzyloxymethyl group.

16. The process according to claim 1

wherein R^2 and R^3 are joined to each other to form a methylene group.

17. The process according to claim 1

wherein the compound (II) or (VI) is optically active.

18. The process according to claim 2

wherein, referring to the acetic acid ester, R^1 represents a tert-butyl group.

19. The process according to claim 2

wherein a magnesium halide is added in permitting the lithium amide to act.

20. The process according to claim 3

wherein a magnesium halide is added in permitting the lithium amide to act.

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